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EXPERT OPINION

Healthcare professional surveys to investigate the implementation of the isotretinoin Pregnancy Prevention Programme: a descriptive study

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Objective: Three online surveys explored compliance with the PPP by pharmacists and dermatologists, in the Netherlands. In 2007 and 2011, two pharmacist surveys were conducted to assess improvement over time.
Methods: In 2007, survey was sent to members of the Utrecht Pharmacy Panel for Education & Research (UPPER) network (n = 1000) and in 2011, to the research group of the Dutch Association of Pharmacists (KNMP) (n = 556). In 2010, a survey was sent to 564 dermatologists of the Dutch Association of Dermatology and Venereology (NVDV).
Results: Both pharmacists' questionnaires had response rates of 20% and the dermatologist questionnaire of 28%. Pharmacists' checks on 30-day dispensing remained 82%, but a check whether the prescription is out-of-date decreased (61 to 53%). Pharmacists asked the patient for a negative pregnancy test in 15%, but use of contraception was checked by 44 – 49%. One hundred and five dermatologists (64%) always prescribe contraception; 35 (22%) occasionally. Ninety-three percent of the dermatologists were of the opinion that they performed the PPP. Analysis of different elements of the PPP showed that 41 (25%) were compliant.
Conclusions: The observed non-adherence to the isotretinoin PPP calls for careful evaluation of risk minimisation plans and participation of all stakeholders in the development of these plans.

Keywords: acne, dermatology, isotretinoin, pregnancy, prevention, surveys

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1. Introduction

The thalidomide disaster in 1961 – 1962 revealed that drugs thought to be relatively safe may disguise a serious risk. This catastrophe increased the awareness of potential adverse reactions to drug exposure, but also the awareness of pharmacovigilance during pregnancy or otherwise. Besides developing systems to collect spontaneous adverse reaction reports due to drug exposure and collecting data for pharmacoepidemiology drug utilisation studies, a more pro-active approach on managing risks has been established, including taking risk minimisation measures, such as a pregnancy prevention programme [1].

Vitamin A derivates are known to be teratogenic. Isotretinoin, a vitamin A derivative has been licensed for the treatment of acne since 1982 in the USA and 1984 in Europe. Despite the fact that the product information of isotretinoin (Roaccutane®, Roche) contained a contra-indication for pregnancy at the time of approval, exposure during pregnancy occurred and congenital anomalies have

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Box 1. Elements of the current EU PPP.

Contraindication pregnant women and women of childbearing potential unless all the conditions of the PPP are met
Medically supervised pregnancy tests before, during and after discontinuation
Two methods of contraception
Educational material physician
Educational material pharmacist
Information patient
Patient information on contraceptive methods
Informed consent form
Restricted supply females of childbearing potential, for 30 days and prescription validity of 7 days

been reported, even if isotretinoin had been taken for short periods of time [2,3]. In 1985, the isotretinoin embryopathy has been first described by Lammer *et al.* [4]. This embryopathy consists of craniofacial, cardiac, thymic and central nervous system (CNS) defects and has a frequency of 26% in exposed patients. In 1988, in order to improve the prevention of pregnancies, Roche introduced a Pregnancy Prevention Programme (PPP) worldwide [5]. Key principles of the isotretinoin PPP are educational material for health care providers and patients, therapy management and dispensing control.

In 2003, generic formulations of isotretinoin entered the European market. In the European Union (EU) a review [6] was performed and the European Commission (EC) decided that an EU PPP should be applicable to all isotretinoin containing products for systemic use. In addition, the indication for use was restricted and imposed elements of the PPP were stricter as well. In the current EU PPP, prescribers, pharmacists and patients are involved to perform this PPP appropriately. The exact roles are laid down in the product information and/or educational material [6]. This PPP was implemented in most EU countries [7]. See **Box 1** for all elements of the current EU PPP.

Pro-active risk minimisation programmes such as the isotretinoin PPP have been developed to prevent undue harm to patients. Effectiveness in reducing risks by measures itself such as the individual elements of these programmes is hardly performed. Studies on the effectiveness of the PPP as a whole indicate that the programme lacks complete effectiveness because pregnancies still occur both in the USA [8] and Europe [9]. Effectiveness of risk minimisation programmes in daily medical practice largely depends on actual compliance with these programmes by the stakeholders. Patients' compliance has been assessed with regard to adherence of contraception requirements in several studies [10-12]. These studies showed that not all women of childbearing potential receiving isotretinoin use one contraceptive method not to mention two methods. Limited information, however, is available on compliance with the current isotretinoin PPP recommendations by pharmacists [13,14] and dermatologists [13]. Therefore, we conducted three surveys among health care professionals and the aim of these surveys was to explore the compliance with the isotretinoin PPP by community pharmacists and dermatologists in the Netherlands. The two surveys among pharmacists have been conducted in 2007 and 2011, allowing us to assess improvements over time. The second pharmacist survey and the dermatologist survey (2010) are part of an investigational programme because of the results of the first pharmacist survey.

2. Materials and methods

2.1 Data collection

Three surveys were performed, two among pharmacists and one among dermatologists.

2.1.1 UPPER network

In 2007, a short online questionnaire was developed for a pilot study and the link was sent once (April 16, 2007) to approximately 1000 community pharmacies who are member of the Utrecht Pharmacy Panel for Education & Research (UPPER) network of the Department of Pharmaceutical Sciences, Utrecht University, the Netherlands. Pharmacists participating in the UPPER network are practising pharmacists. The questionnaire was closed after 2 weeks, because the number of completed questionnaires was higher than anticipated for this pilot study. The structured questionnaire contained a combination of 14 closed and open questions. The questions addressed apart from general issues, more specific items as checks on dispensing, therapy management, perceived responsibility and role of the pharmacist. Demographic characteristics were not collected for this pilot study.

Responders to this survey could provide their e-mail address for information about the outcome of the study. Forty-five percent of the responders did so and these e-mail addresses were all different, indicating that one pharmacist per pharmacy responded.

2.1.2 Dutch association of pharmacists

In 2011, it was decided to repeat the 2007 survey among pharmacists and the questionnaire was amended based on the questionnaire of the UPPER network and consisted of 22 questions. The link to this questionnaire was originally included in a Newsletter of the Dutch Association of Pharmacists, but because of a low response, the link to the questionnaire was sent in addition to the specific research group of the Association (n = 556 practising pharmacists) by e-mail on

April 1, 2011. After three weeks a reminder was sent. The collection period covered a 3-month period from 1 April 2011 through 1 July 2011.

2.1.3 *Dermatologists*

In 2010, a questionnaire was developed consisting of eight questions aimed at dermatologists. An e-mail with a link to this questionnaire was sent to 564 practicing dermatologists and dermatologists in training registered with the Dutch Association of Dermatology and Venereology (NVDV). A reminder was sent once, after six weeks. The response was collected over the period of May 2010 through September 2010. The questions concerned those parts in the PPP dealing with information provision to patients, actions of prescribers and their interaction with patients.

2.2 Compliance definitions

Full compliance with the isotretinoin PPP for pharmacists consists of adherence to dispensing control (dispensing for 30 days, prescription validity of 7 days), provision of educational material and check of availability of negative pregnancy testing and use of contraception at time of every dispensing of isotretinoin to women of childbearing potential.

For dermatologists, full compliance with the PPP consists of providing information on the PPP, prescribing contraceptive measures, performing monthly pregnancy tests and prescribing isotretinoin for a maximum of 30 days.

2.3 Analyses

Duplicates and incomplete questionnaires were excluded from the analyses. Incomplete questionnaires were defined as questionnaires of which the completion was interrupted and therefore were not filled in up to the end. Questionnaires in which some questions were not answered were included, which was defined as missing in the analyses.

Descriptive statistics were performed on the data collected by the questionnaires.

3. Results

3.1 Pharmacist questionnaires 2007 and 2011

3.1.1 *General*

A total of 208 pharmacists participated in the 2007 survey, a response rate of 20%. In most of the pharmacies (69%) less than five patients filled prescriptions for isotretinoin at time of the survey.

A total of 155 questionnaires were filled in the 3-month period in 2011. Eliminating duplicates and incomplete filled responses, 148 questionnaires were included in the analyses consisting of reactions on the Newsletter and the Association research group. Only the response rate of the research group could be determined, because the source population of the Newsletter could not be determined. The response rate of the research group was 20%, 109 out of 556 pharmacists.

In 2011, of the responding pharmacists 61% (n = 90) were female and 39% (n = 58) were male pharmacists. Thirty-nine percent of all pharmacists (n = 57) belonged to the age group of 23 – 35 years of age, 29% (n = 43) to the age group 35 – 45 years of age, 23% (n = 34) to the age group 45 – 55 years of age and 9% (n = 14) to the age group 55 – 65 years of age. Hundred forty-three (97%) pharmacists were working in a community pharmacy. About half of the responders, 51% (n = 76), had less than 5 patients filling prescriptions for isotretinoin.

In 2007, 78% of the pharmacists confirmed that they were aware of the isotretinoin PPP compared with 96% of the responders in 2011, see **Table 1**.

Results reported below are also presented in **Table 1**.

3.1.2 *Distribution control*

Approximately one-third of all pharmacists (32 – 34%) accepted prescriptions from dermatologists only. Most pharmacists (90% in 2007, 84% in 2011) dispensed generic forms of isotretinoin only.

In both surveys the 82 – 83% of the pharmacists indicated that they receive a computer alert reminding them that the prescription of isotretinoin should be limited to a 30-day supply for all female patients at risk of pregnancy. Only 35% never deviated from this rule. Main reasons mentioned for deviation from the requirement were prescriptions for male patients, patient's holidays, on request of the prescriber or unintended ignorance of the computer alert. The 7-day validity of the isotretinoin prescriptions was adhered to by 61% in 2007 compared to 53% in 2011.

Only 15 – 16% of the pharmacists mentioned asking for a negative pregnancy test result before each dispensing of isotretinoin to women of childbearing potential, whereas more than half of the pharmacists stated that they never asked for test results. The use of contraception was checked at time of every dispensing by 44 – 49%, at time of first dispensing only by 20.7% in 2007, but by 33.8% of the pharmacists in 2011.

3.1.3 *Information provision*

Both surveys reported that approximately 10 – 14% did not provide any information on the isotretinoin PPP to women of child bearing potential. Information on contraception was more frequently provided in 2011 than in 2007 (72.3% and 38.9%, respectively).

3.1.4 *Responsibility*

With both surveys, the majority of pharmacists (72 – 74%) considered that the main responsibility for the isotretinoin PPP lies with the prescribers. Others considered a combination of prescriber and either pharmacist or patient or all of them primarily responsible for the programme. On the other hand, 63.5% of the pharmacists in 2007 agreed they should play a role in monitoring the isotretinoin PPP in the surveillance or otherwise, which was even higher in 2011 (82.4%), although 12.8% added objections.

Table 1. Results on responses by both pharmacists' surveys and the dermatologist survey.

	UPPER Network 2007 n = 208 (%)	Dutch Association of Pharmacists 2011 n = 148 (%)	Dermatologists 2010 n = 161 (%)
General			
Number of patients on isotretinoin at time of the survey			
< 5	143 (68.8)	76 (51.4)	
5 – 10	50 (24.0)	54 (36.5)	
11 – 20	12 (5.8)	12 (8.1)	
> 20	3 (1.4)	6 (4.1)	
Are you aware of a Pregnancy Prevention Programme for isotretinoin?			
Yes	163 (78.3)	142 (95.9)	152 (94,4)
No	18 (8.7)	6 (4.1)	9 (5.6)
Missing	27 (13.0)		
Distribution control			
From which prescribers do you accept a prescription for isotretinoin?			
Dermatologist	70 (33.7)	48 (32.4)	
Dermatologists, GP and/or gynaecologist	44 (21.6)	42 (28.4)	
All physicians	86 (41.3)	58 (39.2)	
Does your pharmacy system provide an alert on the maximum of 30 days per prescription?			
Yes	172 (82.7)	121 (81.8)	
No	25 (12.0)	27 (18.2)	
Missing	11 (5.3)		
Do you deviate from this rule?‡			
Never	71 (34.1)	53 (35.8)	80 (49.7)
Rarely	38 (18.3)	46 (31.1)	61 (37.9)
Regularly	37 (17.8)	6 (4.1)	
Only in exceptional circumstances	43 (20.7)	42 (28.4)	
Missing	19 (9.1)	1 (0.7)	3 (1.9)
Do you check the validity of 7 days for a prescription of isotretinoin?			
Yes	127 (61.1)	79 (53.4)	
No	66 (31.7)	25 (16.9)	
Only in exceptional circumstances		44 (29.7)	
Missing	15 (7.2)		
Providing information			
To whom do you provide information regarding the PPP of isotretinoin?			
All patients	45 (21.6)	34 (23.0)	
Women of childbearing potential	121 (58.2)	91 (61.5)	
Others	9 (4.3)	2 (1.4)	
No additional information will be provided	22 (10.6)	21 (14.2)	
Missing	11 (5.3)		
Which brochures will be provided?			
On isotretinoin			
Yes	163 (78.4)	127 (85.8)	
No	45 (21.6)	21 (14.2)	
On contraceptive methods			
Yes	81 (38.9)	107 (72.3)	
No	127 (61.1)	41 (27.7)	
Other information			
Yes	3 (1.5)	107 (72.3)	
No	205 (98.5)	41 (27.7)	
Additional oral information?			
Yes	120 (57.7)	108 (73.0)	

*Contraception will be prescribed by 105 responders (65%), but including those who first check before prescribing or refer patients to a gynaecologist or GP it will be 140 responders (87%).

‡Dermatologist had the option to answer 'always' (n = 17), which is not covered by the options presented.

§12.8% of these pharmacists added objections.

NA: Not Applicable.

Table 1. Results on responses by both pharmacists' surveys and the dermatologist survey (continued).

	UPPER Network 2007 n = 208 (%)	Dutch Association of Pharmacists 2011 n = 148 (%)	Dermatologists 2010 n = 161 (%)
No	29 (13.9)	39 (26.4)	
Missing	59 (28.4)	1 (0.7)	
Responsibility			
Who is responsible for the PPP?			
Prescriber	150 (72.1)	110 (74.3)	4 (2.5)
Specific arrangements	11 (7.3)	10 (6.8)	
No specific arrangements	139 (92.7)	100 (67.6)	
Pharmacist	9 (4.3)	9 (6.1)	
Patient	10 (4.8)	11 (7.4)	40 (24.8)
Otherwise	25 (12.0)	18 (12.2)	
Combination prescriber and pharmacist	14 (56.0)	10 (55.6)	NA
Combination prescriber and patient	4 (16.0)	2 (9.0)	117 (72.7)
Combination prescriber, pharmacists and patient	6 (24.0)	6 (33.3)	NA
Regulatory authority and pharmaceutical industry	1 (4.0)		NA
Missing	14 (6.7)		
Compliance with the PPP			
Do you check the following?			
Negative pregnancy test			
First dispensing/prescription	27 (13.0)	32 (21.6)	145 (90.0)
Each dispensing/prescription	32 (15.4)	23 (15.5)	104 (64.6)
Never	106 (51.0)	92 (62.2)	12 (7.5)
Missing	43 (20.7)	1 (0.7)	3 (1.9)
Contraceptive use			
First dispensing/prescription	43 (20.7)	50 (33.8)	105 (65.2)/140 (87.0)*
Each dispensing/prescription	91 (43.8)	72 (48.6)	
Never	41 (19.7)	26 (17.6)	
Missing	33 (15.9)		
Has the pharmacist a controlling function regarding the PPP?			
Yes	132 (63.5)	122 (82.4)[§]	
No	56 (26.9)	26 (17.6)	
Missing	20 (9.6)	19 (12.8) 'otherwise'	

*Contraception will be prescribed by 105 responders (65%), but including those who first check before prescribing or refer patients to a gynaecologist or GP it will be 140 responders (87%).

[‡]Dermatologist had the option to answer 'always' (n = 17), which is not covered by the options presented.

[§]12.8% of these pharmacists added objections.

NA: Not Applicable.

3.1.5 *Compliance with the PPP (not in Table 1)*

In both surveys, only a limited number of pharmacists, 6.7% in 2007 and 8.8% in 2011, fully complied with all aspects of the isotretinoin PPP. Pharmacists complying with all aspects of the dispensing control element that is part of the isotretinoin PPP as stated in the methods section consisted of 39% in both groups.

In 2011, pharmacists were asked for suggestions to increase the compliance with the PPP. Suggestions received were: oblige prescriber to prescribe contraceptives together with drugs like isotretinoin, better communication, better information tools, informed consent form for patients to be signed at the pharmacy, to improve the pharmacy monitoring systems, to have stickers with warnings for drugs like isotretinoin and unambiguous policy on responsibility of the individual stakeholders of such programmes.

3.2 Dermatologists

3.2.1 *General*

Hundred-sixty one out of the 564 surveyed dermatologists and dermatologists in training completed the questionnaire, a response rate of 28.5%. Results reported below are presented in **Table 1**.

Responders were aware of the PPP of isotretinoin through their professional association in 35%, followed by the pharmaceutical industry (12%), literature (4%) or the product information of isotretinoin (2%). Most of the responders received the information through a combination of the different sources (41%). Nine dermatologists (6%) indicated not to be aware of the PPP.

3.2.2 *Providing information*

Time needed to inform the patient and performing the other PPP elements for prescribers took the responders mostly

Table 2. Self-reported adherence to (elements of) the PPP by dermatologists (n = 161).

Question	Always n (%)	Sometimes n (%)	Never n (%)	Missing n (%)
Execution PPP as entirety	150 (93)	– (0)	8 (5)	3 (2)
Separate elements				
Signing informed consent form	112 (70)	31 (19)	15 (9)	3 (2)
Performance of pregnancy tests	104 (65)	41 (25)	12 (7)	4 (2)
Monthly prescriptions	79 (49)	61 (38)	16 (10)	5 (3)
Regular prescriptions contraceptive	82 (51)	65 (40)	10 (6)	4 (2)

5 min (35%), or less (34%). Three responders mentioned that either a nurse or a physician assistant performed these tasks.

3.2.3 *Responsibility*

According to 117 responders (72.7%), the responsibility for pregnancy prevention should be a shared responsibility by both prescriber and patient. Forty responders (24.8%) considered the patient solely responsible for the adherence to the PPP. Four responders considered it completely their responsibility (2.5%).

Furthermore, 10 responders (6.2%) informed the patient about the risks but stated that pregnancy prevention was the patient's responsibility.

3.2.4 *Compliance with the PPP*

Hundred-five responders (65%) also prescribed contraceptives. In addition, 35 dermatologists (22%) mentioned that they prescribed contraceptives after checking whether the patient is already on contraception or refer patients to a gynaecologist or general practitioner for contraception. Ten responders (6.2%) mentioned that they would not prescribe a contraceptive for patients indicating to be not sexually active, for instance in case of religious reasons.

Ninety-three percent of the dermatologists were of the opinion he/she adhered to the PPP, see **Table 2**. Breaking down the PPP to the specific elements for dermatologists, it seemed that only 41 (25%) of the responders adhered to the PPP. Of the 115 responders who agreed on the current PPP, 34 (29.5%) adhered to all elements of the PPP. But 7 of the 46 responders (15.6%) not in agreement on the current PPP or the need of a PPP, adhered to the PPP (not in **Table 2** as will be also the following results).

Forty-five responders (28%) experienced no problems with adherence to the PPP. Problems on adherence to the PPP were reported by 72% responders. Patient related problems were for instance refusal to use contraceptives due to religion. A concern mentioned by dermatologists was possible under treatment of patients due to refusal of isotretinoin because of the PPP.

3.2.5 *Proposals for change or improvement*

Hundred-fifteen (71%) of the responders agreed with the need for a PPP for isotretinoin. Reasons for disagreement were that the PPP were unnecessary (n = 6), no difference compared to other products with a contraindication for use during pregnancy (n = 6), responsibility of the patient after providing information (n = 5). The other reasons addressed discontent instead of disagreement too strict (n = 10), patronising (n = 9), time consuming (n = 2) and single arguments such as it will cause concerns, cause an unnecessary threshold, there is no 100% guarantee, too interfering, too many exceptions and too general.

Proposals for change or improvement of the PPP by the physicians were given by 75 (47%) of the responders. Proposals ranged from abolition of the PPP to have a more clear information package. Changes proposed more than once were:

- The prevention of pregnancy is only patients' responsibility
- To extend the prescription and control intervals
- To execute the PPP based on judgment of the situation
- To abolish the mandatory pregnancy tests
- To have a patient contract by which it is clear that pregnancy prevention is the responsibility of the patient
- To have a guideline/advice instead of the obligation, which can also be used for other drugs with a contraindication for pregnancy

Other proposals were for instance to have GPs or nurses performing the monthly controls, return to the old less restricted PPP, discarding of the informed consent form, exclude the actions for the pharmacist (control of the restricted prescription for 30 days, and delivery within 7 days of the date of prescription).

4. Discussion

According to the majority of Dutch community pharmacists as well as dermatologists, the main responsibility for the isotretinoin PPP should be either with the prescribers or a joint responsibility of prescriber and patient. In general, community pharmacists acknowledge their role of monitoring the isotretinoin PPP; however, the programme requirements are not fully adhered to in daily medical practice. Only two out of five pharmacists adhered to all requirements concerning

dispensing control, and < 10% reported full compliance with all the elements of the isotretinoin PPP. Adherence of the pharmacists was especially poor in terms of supervision of use of contraception and check of negative pregnancy test results. And adherence did not improve over time even though the PPP has been brought to the attention of pharmacists during this period.

Adherence to the PPP seemed somewhat better by dermatologists. However, monthly prescriptions and prescribing of contraceptives were poor. The dermatologists considered themselves more responsible for the execution of the PPP than the pharmacists. Prescribers were more alert regarding pregnancy tests and contraceptive use.

The response rates to the questionnaires are a limitation of the study. It is possible that only motivated health care professionals responded. If so, our results may present a more positive view about the adherence to the PPP. However, response rates of online surveys among pharmacists and physicians might range from 3.1% [15,16] to 75% [17,18], but are mostly between 30 – 40%. A recent publication [19] shows that response rates to web-based questionnaires are becoming comparable to those responding to traditional modes of data collection. Therefore, mode of distribution of the questionnaire might not be the reason for this response rate.

Community pharmacists who belong to the UPPER network of Utrecht University and the research group of the Dutch Association of Pharmacists may represent a selected group of pharmacists as they belong to these groups because of their interest in pharmaceutical practice research and/or because they offer internships to pharmacy students. However, both groups consist merely of community pharmacists and were recruited in a similar way. The instructions for completion of the questionnaire circulated to pharmacies of the UPPER network did not contain instructions for completion (on behalf the pharmacy or personal opinion), which could be regarded as a limitation. Another limitation of the present study is that responses to questions in the surveys could not be validated. As a consequence, all results reflect pharmacists' or dermatologists' self-reported behaviour. It can therefore not be ruled out that performance of Dutch community pharmacies and dermatologists in general may even be more disappointing. For instance, almost all (93%) of the responding dermatologists thought they adhered to the PPP, but taking into account individual elements of the PPP for prescribers, only a quarter adhered to the PPP as stated in the product information. A limitation is also the omission in the dermatologists' survey to have pharmacists as an option for having a responsibility for the PPP.

Evaluation of implementation of risk minimisation programmes in daily practice is important, because weaknesses might be revealed and could be corrected. Medical literature on this subject is scarce, whereas knowledge on implementation and effectiveness of risk minimisation programmes is essential to achieve full benefits from these programmes. Regulatory authorities may learn from the gaps identified in the present study for future programmes.

No information is available on adherence to the dispensing control element (restriction to 30-day supply and 7-day validity) of the isotretinoin PPP in the Netherlands or in other European countries. Boucher *et al.* [20] reported that Canadian pharmacists had given verbal information about teratogenicity and pregnancy prevention to 78% of the women participating in their survey. In addition, pharmacists gave written information other than the package insert to 62% of the women filling their isotretinoin prescription. These results are similar to the results presented in this study. Although our pharmacist surveys did not focus on the physician's role in adherence to the programme, several pharmacists reported that they filled prescriptions that were not limited to 30 days of treatment at physicians' request. In addition, several pharmacists reported that patients presented undated prescriptions. Regretfully, the performance of the PPP by pharmacists did not improve over the years based on the results of both our pharmacists' surveys.

Previous studies showed that the physician's adherence to the isotretinoin PPP should be improved. A retrospective cohort study [21] assessing documentation of use of contraception or recent contraceptive counselling in the USA in 2001, the year before institution of the SMART risk management programme, showed that documentation was available in only 62% of isotretinoin prescriptions filled. A more recent US study [22] showed that 9% of qualified prescriptions as part of the SMART programme were issued without a pregnancy test. In addition, a cross-sectional Canadian survey [21] showed that pregnancy testing was poor before and during (every month of) isotretinoin use (44% and 13%, respectively). In this survey, a direct relationship between counselling and recommendations given by physicians and women's use of two forms of birth control was established.

Our study suggests that risk management programmes may be supported with provision of educational material to healthcare professionals. Physicians prescribing isotretinoin for the first time and new pharmacists should therefore also be informed about the isotretinoin PPP. Our data suggest that new physicians prescribing isotretinoin may include others than dermatologists alone, and therefore provision of information should not be limited to dermatologists. Enduring awareness of the PPP recommendations and their underlying principles should be maintained among healthcare professionals, and for pharmacies computer alerts seem a helpful tool to achieve this awareness.

One of the interesting results of the present surveys among Dutch community pharmacists and dermatologists is the acknowledgement of their own role in conducting the isotretinoin PPP. At the same time the fact that pharmacists attribute the main responsibility for the compliance with the programme to the treating physicians. This is confirmed by the dermatologists who acknowledged their responsibility alone

or sharing it with the patient. This finding may explain why only a minority of pharmacists (15.4%) reported that they asked for pregnancy test results before every dispensing of isotretinoin to fertile women. Responsibilities are not explicitly laid down in the current isotretinoin PPP and this might be a key issue in the development of new PPPs by the regulatory authorities.

A more proactive approach towards the identification and quantification of safety concerns after marketing has been implemented in the EU in November 2005 by the obligatory submission of an EU Risk Management Plan (EU-RMP). Part of the RMP should evaluate the need for risk minimisation activities and, if considered needed, a description of these activities. Proposals for risk minimisation activities other than pregnancy prevention programmes, for example, monitoring of laboratory measurements, may also require specific physicians' and pharmacists' achievements and behaviour. The observed non-adherence to the isotretinoin PPP calls for careful evaluation of proposed risk minimisation plans and participation of all stakeholders in the developmental phase of these plans.

5. Conclusion

According to the majority of Dutch community pharmacists as well as dermatologists, the main responsibility for the isotretinoin PPP should be either with the prescribers or a joint responsibility of prescriber and patient. Although pharmacists acknowledge their role in monitoring the isotretinoin PPP, requirements of this programme are adhered to a limited extent in daily pharmaceutical practice. Dermatologists' actual adherence to the elements of the PPP is inadequate. Pharmacists and prescribers could enhance the compliance with the PPP by working together and so complementing each other. Prescribers consider female patients responsible for preventing pregnancy and therefore they should provide the conditions to ensure the highest possible compliance by the patients. These findings are important in view of future programs. Reinforcement of the current isotretinoin PPP is warranted.

6. Expert opinion

According to dermatologists, oral isotretinoin is the most effective drug to treat acne. Therefore, despite its high risk of human teratogenicity by a treatment indication which is not life-threatening there is a need for this drug. This high risk of human teratogenicity is a burden for the pharmaceutical company and regulatory authorities, which has lead to successive PPPs.

Ultimately, effectiveness of the isotretinoin PPP should be reflected in decreasing numbers of pregnancies exposed to isotretinoin. A systematic literature review [23] on studies regarding the implementation and adherence to the isotretinoin PPP showed that few studies were performed in Europe. Successively performed studies in France on data collected over the period 1987 up to and including 2006 showed that despite strengthening of the programme, the pregnancy rate did not change. All identified studies evaluated the compliance with the PPP of isotretinoin in their respective countries. A common conclusion of all studies/surveys was that the compliance was regarded insufficient and that the PPP should be strengthened. The case reports indicate that pregnancies occurred despite a PPP for isotretinoin was adhered to. In the USA, similar results are seen; evaluation [24] of the SMART programme showed that pregnancy rate for patients participating in the pharmacy compliance survey was comparable to that reported before this programme. Evaluation [8] of the even stricter programme iPLEDGE showed a similar pregnancy rate as with the previous SMART programme. Reinforcement of the present isotretinoin PPP, however, seems warranted and should involve all stakeholders including pharmaceutical companies, regulatory authorities, physicians, pharmacists and patients.

Investigations to the effectiveness of the PPP for other products, such as thalidomide and lenalidomide, have been done by the pharmaceutical company itself. These studies focused on the occurrence of pregnancies, but also on the adherence to the programme by healthcare professionals and/of patients. It has been suggested that medical specialists would have a better adherence to the PPP than general practitioners. However, in a drug utilisation study [12] on isotretinoin it was indicated that general practitioners had a better performance.

A recent survey conducted among dermatologists in Saudi Arabia [25] showed also that some dermatologists are not compliant with recommendations for isotretinoin use in women of childbearing potential. This study is one of the few studies performed among dermatologists and the actual adherence to the PPP.

Based on our study, information of the performance by the actual executioners of risk minimisation measures is collected. This information indicates that some aspects of the execution, mainly concerning personal feelings and views can stand in the way of proper performance or full adherence of these measures.

In principle, the PPP fails with every pregnancy exposure occurring. Based on studies performed on the isotretinoin PPP other possible failures were: no 100% contraceptive use in female isotretinoin users; the majority of dermatologists do not perform all the tasks of the PPP; and the majority of pharmacists also lack adherence to their tasks of the PPP. Regarding the latter, pharmacists and prescribers could enhance the compliance with the PPP by working together and so complementing each other.

The studies and surveys on the isotretinoin PPP seem to point in the direction of the patient and the possible insufficient compliance with contraception. This might be obvious, because that is the end of the chain before getting pregnant. However, the PPP should be a shared responsibility and conditions to be compliant with contraception, preventing

pregnancy, should be provided by all stakeholders including authorities, prescribers, pharmacist and patients.

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Declaration of interest

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